HEMANGIOPERICYTOMA

A VASCULAR TUMOR FEATURING ZIMMERMANN'S PERICYTES

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IN A RECENT COMMUNICATION, the writers demonstrated by the method of tissue culture that the epithelioid cell of the glomus tumor is derived from Zimmermann's pericyte. This is a contractile cell with long processes which wraps itself about capillaries and serves to change the caliber of their lumens. Zimmermann, and others, have suggested that these pericytes are modified smooth muscle cells. The glomus tumor is a complex organoid neoplasm furnished with many axis cylinders, which reproduces in caricature the normal neuromyo-arterial glomus. There occur, however, tumors composed of capillary blood vessels with one or more layers of rounded cells arranged about them, which cannot be called glomus tumors because they lack the organoid features of those encapsulated complex neoplasms, yet differ from simple capillary hemangiomata because of the presence of their perivascular cells. We believe that these cells are pericytes and that these tumors should be distinguished by a specific name and suggest "hemangiopericytoma" as properly descriptive.

In the past, one gathers that such tumors have generally been called hemangio-endotheliomata on the assumption that only the prolific and versatile vascular endothelia could give rise to these rounded perivascular cells. We have never agreed with this opinion but had no alternative suggestion for their origin until we learned about pericytes from the writings of Zimmermann and observed how greatly they differed from endothelia when grown *in vitro*. There are, indeed, vascular neoplasms that may properly be called hemangio-endotheliomata. These are malignant tumors of capillaries featuring the growth of neoplastic endothelia, which in addition to heaping up inside the lumen may invade the wall and proliferate outside but these tumors are very different from hemangiopericytomata in which the endothelia never differ from the appearance of normal endothelial cells.

It is probable also that Schmidt (1937) has included one or possibly two cases of hemangiopericytoma in a group if vascular tumors which, following the suggestion of Orsós (1934), he chooses to call gemmangiomata. Orsós revived the hypothesis of R. Meyer that blood vessels and blood cells are all derived from embryonal pluripotent cells called angioplasts. He then proceeded to describe a number of vascular tumors, some composed in part of capillaries and in part of immature endothelial sprouts without lumens and others

much more complex with both capillaries and immature red and white blood cells. Orsós also included tumors which did not seem primarily vascular at all, and in attempting to follow his lead Schmidt included under the name gemmangioma tumors which seem to us to be xanthoma and liposarcoma. If Orsós had restricted the term gemmangioma to tumors composed of immature capillary sprouts, the term might be acceptable. But since he has chosen to make it cover a heterogeneous variety of tumors which Schmidt has further enlarged, we believe that only confusion will follow any attempt to perpetuate the term.

In our collection of 691 blood vessel tumors, we find nine cases to which the name hemangiopericytoma may be applied in addition to 38 glomus tumors for which the term might also be used. This group of nine tumors is an interesting one because it includes cases showing most of the biologic features exhibited by other vascular tumors including locally persistent aggressive infiltrative growth in one instance and distant metastasis resulting in death in another. In another crucial case, the probable relationship between pericyte and smooth muscle cell is strongly suggested because the cells arranged about the tumor vessels vary all the way from the usual rounded pericyte through an indeterminate phase of spindle shapes to a fully differentiated cell with myofibrils.

The first four cases are all alike histologically, and demonstrate the usual appearance of this neoplasm:

CASE REPORTS

Case 1.—A male, age 45, had a tumor the size of a dressmaker's pin on the dorsal surface of the left ring finger. It looked like a nonpigmented mole. If struck it would bleed and become sore, otherwise it gave no trouble. After an attempt to destroy it by electrocauterization failed, it was excised. Three years later there was no evidence of recurrence. (Case made available by Dr. F. A. Patterson of Norwalk, Conn., and Dr. Gray Twombly, New York.)

Case 2.—When this female infant was born, a small "birthmark" was noted in the skin at the outer margin of the breast. It was excised at the age of six months. The case was not followed. (Case made available by Dr. Howard Meyer, Hackensack Hospital, N. J.)

Case 3.—When this female infant was born, there was a small red spot in the skin of the parietal region. At age three months it had reached a diameter of 1 cm. and was excised. It was quite vascular but did not extend beneath the galea. The case was not followed. (Case made available by Dr. A. O. Severance, San Antonio, Texas.)

Case 4.—Age and sex unknown. Five months before, a blow was received on the shoulder and another one two months later. Following this a lump appeared in the skin and grew larger. It was tender, attached to the skin but otherwise freely movable. It was excised and the case was not followed. (Case made available by Dr. H. Meyer, Hackensack Hospital, N. J.)

Pathologic Characteristics.—All of these tumors are made up of groups of endothelial-lined tubes filled with erythrocytes and of endothelial sprouts without lumens. Both are supported by delicate reticulin fibers outside of which are arranged the rounded pericytes. These sometimes form a single layer or they may be in such numbers that all of the space between neighboring vessels may be filled with them. Some vessels may have no pericytes. No elastic fibers are formed. Like ordinary capillary hemangiomata,

the groups of tumor vessels infiltrate the skin and sometimes the subcutaneous fat to a limited degree (Fig. 1).

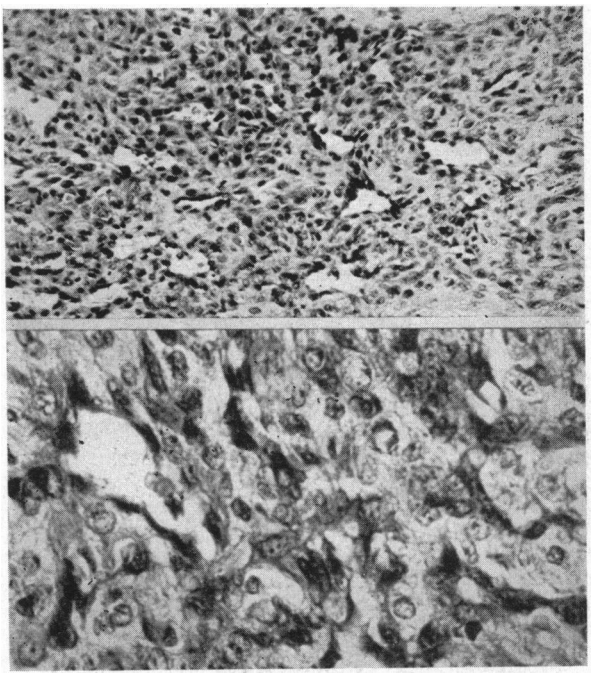

FIG. 1.—Case 1: Above, is shown one of the nodules composed of endothelial-lined capillaries surrounded by masses of pericytes. Below, a detail enlargement from another area showing endothelial sprouts both with and without lumens. The endothelia are deeply stained and are in sharp contrast with the rounded pericytes which are paler and have vacuolated cytoplasms.

The second group includes cases with both rounded and spindle-shaped cells:

Case 5.—At birth, this male infant had a painless nodule, 17x10 Mm., in the right anterior chest wall which did not increase in size. It lay within the pectoralis major muscle and was excised at the age of two months. The case was not followed. The specimen showed a central area of necrosis surrounded by a grayish-white zone of viable tissue, which invaded the muscle to a limited extent. (Case made available by Dr. Beryl Paige, Babies Hospital, N. Y.)

Case 6.—Male. At age 21, his right infra-orbital region was hit with a nail. In a few days a tumor appeared and grew slowly. Three years later it was excised but promptly recurred, and at age 25, it was again incompletely excised. It then grew slowly for 17 years, and more rapidly during the succeeding three years. At age 45, 24 years after onset, it was 4 cm. in diameter. It was soft, not tender and had never been painful. It lay 1 cm. beneath the epidermis, was apparently encapsulated, and extended into the orbit. The cut surface was pale pink, soft, homogeneous, and mottled with hemorrhages. The case was not followed.

Case 7.—Male, age 31. There was a nodule covered with epidermis, pedunculated, and 5 Mm. in diameter, which projected from the auricle and had been present since childhood. There had been recent slight increase in size but no pain. It was excised and the case was not followed.

Pathologic Characteristics.—In Case 5 the tumor is made up of lobules composed chiefly of endothelial-lined tubes often containing erythrocytes. Arranged in close proximity to the endothelia are rounded pericytes in many areas. In some, however, the cells are spindle-shaped and suggest the appearance of smooth muscle but usually lack myofibrils. In several areas, however, it is possible to trace a direct continuity between these elongated cells without myofibrils and characteristic, mature smooth muscle cells with definite myofibrils. Transition forms containing immature myofibrils can be identified (Fig. 2). Case 6 is like Case 5, but no myofibrils can be found and there are no transitions from spindle cells to smooth muscle cells. Case 7 has very few rounded pericytes and is composed largely of spindle-shaped cells which are heaped up in considerable numbers so that the endothelial-lined tubes are often quite widely separated.

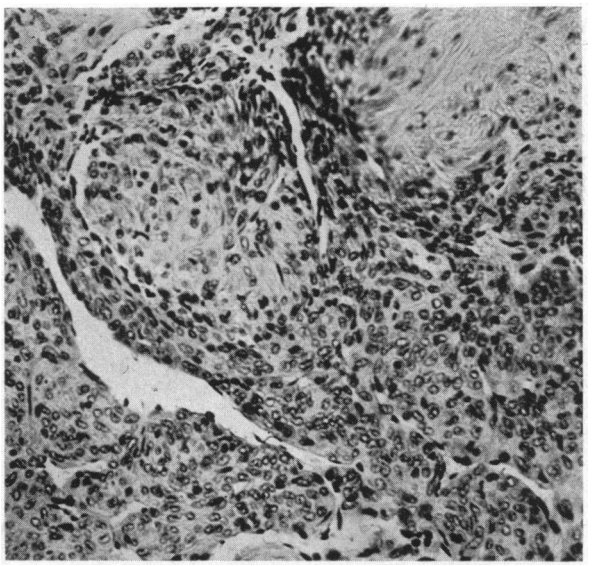

FIG. 2.—Case 5: Numerous endothelial-lined capillaries are surrounded by rounded pericytes. In places, these blend with elongated cells which approximate the appearance of smooth muscle cells.

These three cases seem to us to be of importance because they suggest very strongly that the pericyte is a modified smooth muscle cell. The next step in differentiation would be to have no rounded pericytes but only spindle-shaped cells, some of which were without myofibrils, while the majority were fully differentiated smooth muscle cells. Such tumors exist and have been reported by one of us (A. P. S.) in a paper on cutaneous leiomyomata. They were there called vascular leiomyomata, and the fact that some of the cells contained no smooth muscle fibers was not brought out because its importance was not appreciated. The large amount of smooth muscle formed in the spaces between the vessels was the reason for calling these tumors leiomyomata, but there is no doubt that they are related closely to this present group of hemangiopericytomata.

The next case shows that tumors of this class can exhibit aggressive, infiltrative growth bordering on malignancy:

Case 8.—Male. At age 42, a small tumor appeared on the lateral aspect of the left index finger. This ruptured spontaneously, with a bloody discharge. During the next 11 years he had ten local operations in attempting to remove all of the tumor, but none succeeded. It always reappeared, extending slowly toward the base of the finger and forming multiple nodules. At age 53, the finger was disarticulated at the metacarpophalangeal joint. The tumor reappeared in the stump, and a year later the cicatrix together with the distal three-fourths of the index finger metacarpal bone was resected. This was successful in removing all of the tumor. He was seen 14 years later, without evidence of neoplasm and finally died of an unreported cause at age 70, 28 years after the tumor first appeared, and 16 years after the last operation.

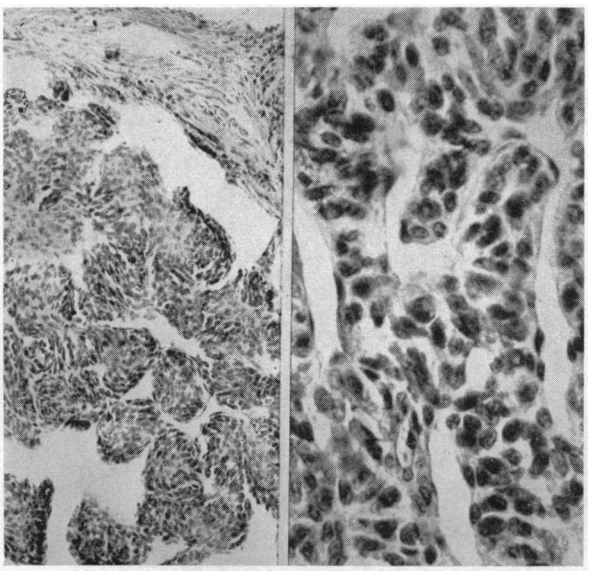

FIG. 3.—Case 8: Appearance of the tumor in the stump of the amputated finger. At the left, a nodule of tumor with its endothelial tubes surrounded by pericytes. At the right, a detail in higher magnification.

In this tumor the pericytes are always the most conspicuous feature of the growth (Fig. 3). Capillaries and endothelial sprouts are present but as the sprouts are not canalized they are inconspicuous and can easily be overlooked. Nevertheless, they are always formed and the tumor grows characteristically in lobules made up of aggregations of vessels and sprouts with their satellite cells. Grossly, the tumor nodules were soft and pallid, presumably because they contained so little blood. Unfortunately, the tissue obtained from this tumor was never properly fixed and our cytologic studies leave much to be desired.

The last case is an example of late metastasis and death in a hemangiopericytoma that exhibited a number of interesting variations in the primary growth:

Case 9.—Colored female. At age 34, she first noted a swelling on the medial aspect of the lower part of the right thigh. This grew considerably during the next three years until, finally, it became slightly painful on walking and its bulk caused slight limitation

of motion at the knee joint. It was excised at age 37. The tumor was irregularly ovoid and measured 14x7x6 cm. It was intimately attached to the periosteum of the anterior aspect of the femur between the condyles and to the mesial aspect of the capsule of the knee joint. Throughout the rest of its extent, it was enclosed by a capsule. The tumor

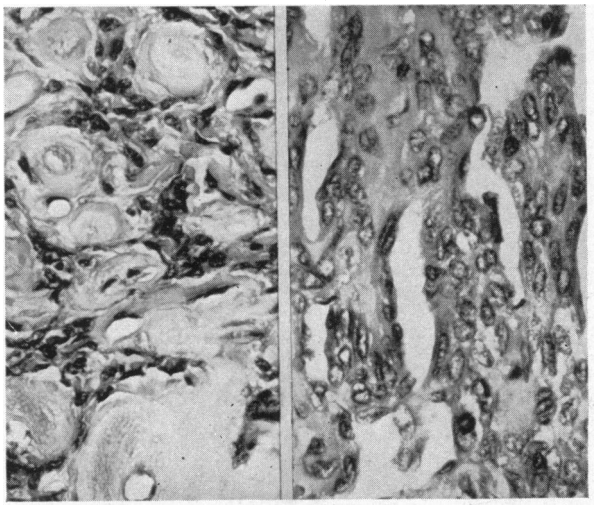

FIG. 4.—Case 9: Detail from the primary tumor. At the right, endothelial tubes and pericytes, without much fibrosis. At the left, the capillaries are surrounded by dense, thick collagen sheaths and the pericytes pushed aside and atrophic.

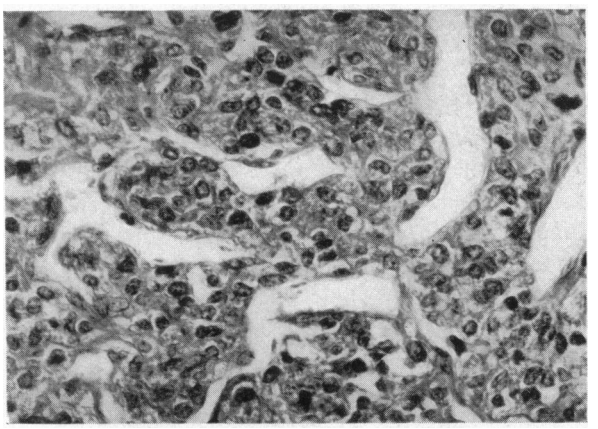

FIG. 5.—Case 9: Metastasis in the liver. The tumor maintains the relationship of capillary tube and surrounding pericytes but the fibrous elements are much less.

was composed of many pale and reddish nodular masses. There was never any local reappearance but four years later there were found five nodules in the right lobe of the liver, varying from 1 to 4 cm. in diameter and one of them was biopsied. The iliac and celiac nodes were enlarged. The liver was treated postoperatively with small doses of roentgenotherapy, with relief of pain. Seventy-four months after the first operation there was roentgenographic evidence of metastases in the third and fifth ribs, and these also received roentgenotherapy. She went progressively downhill, and finally died seven years and four months after the first operation, and three years and four months after proof of liver metastases. No autopsy was done.

Pathologic Characteristics.—Histologically, the primary tumor is composed of capillary tubes and sprouts which in some areas are surrounded by layers of rounded and occasionally elongated cells in the customary fashion. Where recent growth has occurred, the capillaries are simple endothelial tubes supported by reticulin fibers, but where the tumor is older, the endothelia are surrounded by thick compacted collagen sheaths of a hyaline aspect in ordinary stains and the tumor cells are outside of these (Fig. 4). The growth of pericytes, occasionally, is so massive that the vessels are widely separated but, as a rule, the vascular nature of the tumor is never in doubt. No myofibrils are recognized in any of the tumor cells. Laidlaw stains show a rich reticulin framework which surrounds most of the tumor cells.

The vascular aspect of the tumor is clearly shown in the liver metastasis, which is composed of many endothelial tubes surrounded by rounded cells so closely placed that the tumor cells of one unit often touch those of its neighbors (Fig. 5). Most of the tumor cells are surrounded by delicate collagen or reticulin fibers. The aspect of this metastasis closely resembles parts of the original tumor and, histologically, does not appear like a malignant growth.

The hemangiopericytoma thus emerges as a tumor which does not have sufficiently arresting gross features to enable one to recognize it clinically. Except in Cases 2 and 3, in which the tumors involved the skin and resembled other congenital hemangiomata, there is no red color nor are there other gross characteristics suggesting that the growth is one of blood vessels. This is due apparently to the accumulation of pericytes and connective tissue in which the vascular tubes are incased and also to the fact that many of the endothelial sprouts are not canalized and contain no erythrocytes. Otherwise, it behaves very much like other angiomatous tumors in its tendency to begin before birth or early in life, to grow locally sometimes as a circumscribed nodule, sometimes with slow and limited infiltration of surrounding tissues, occasionally with more persistent and aggressive infiltration and rarely with metastasis. Although usually small, it may attain a very considerable size, up to a length of 14 cm. as is shown by Case 9.

The diagnosis can be made by histologic examination. The tumor must be composed of groups of endothelial-lined tubes or impervious endothelial sprouts surrounded by rounded cells with a supporting meshwork of reticulin fibers. The rounded cells may show a tendency to become elongated and in this form poorly defined myofibrils may be found. Usually, the vessels with their pericytes are distinct one from the other, separated by a fibrous stroma, but they may become so closely packed that the pericytes of one vessel may be in continuity with those of its neighbors. One should be very certain, however, that the growth is basically vascular and not a tumor whose cells are nourished by a rich vascular network such as one sees in many tumors of endocrine organs, in some Ewing tumors of bone marrow, and elsewhere.

SUMMARY

A type of vascular tumor has been described, characterized by the formation of endothelial tubes and sprouts with a surrounding sheath of rounded and sometimes elongated cells. The writers believe that these are derived from the capillary pericytes, described by Zimmermann, and suggest that the tumors be called hemangiopericytomata.

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